PATENT SPECIFICATION (11) 1 501 797

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(21) Application No. 22400/74 (22) Filed 28 May 1976
(31) Convention Application No. 7 517 007
(32) Filed 30 May 1975 in
(33) France (FR)
(44) Complete Specification published 22 Feb. 1978
(51) INT CL² C07D 495/04; A61K 31/435
(52) Index at acceptance
C2C 1341 151X 214 215 220 226 22Y 246 247 250 251 256 25Y 280 281 28X 290 29X 29Y 304 30Y 313 31Y 332 338 339 340 342 34Y 351 355 35X 35Y 360 362 364 366 368 36Y 37X 380 388 396 401 40Y 43X 491 577 594 613 615 621 623 624 625 627 628 62X 644 655 658 662 665 672 675 67X 681 682 72Y 751 752 75X 76X 775 780 790 79Y BC KA KP MM QL SN UH UL WC

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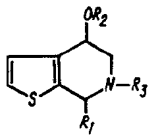
(54) IMPROVEMENTS IN OR RELATING TO TETRAHYDRO THIENO-PYRIDINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THERAPEUTIC COMPOSITION CONTAINING SAME

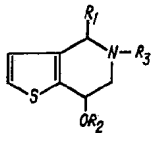
(71) We, PARCOR, a French Body Corporate of 60. rue de Wattingnies, 75579 PARIS CEDEX 12, France, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to new tetrahydrothieno-pyridine derivatives, to a process for their preparation and to their applications in human and veterinary medicine.

The new compounds of this invention have one or the other of the following formulae:



(I)



(II)

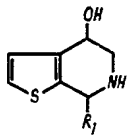
in which R_1 represents hydrogen or an alkyl group having 1—6 carbon atoms; R_2 represents hydrogen or a carboxylic acyl or alkylamino-carbonyl group; and R_3 represents an alkyl of 1—18 carbon atoms, or aralkyl (e.g. benzyl) group optionally substituted with at least one ester, oxo or nitrile group, halogen atom or alkoxy or nitro group; a carboxylic acyl radical optionally substituted with at least one halogen atom or amino, alkoxy, phenoxy, chlorophenoxy or pyrrolidino group; or a sulfonyl, aminocarbonyl or aminothiocarbonyl group.

R_2 may typically be selected from hydrogen, the acetyl group and a lower (C_{1-4}) alkyl-carbamoyl group.

R_3 may typically be a lower (C_{1-4}) alkyl, nitrobenzyl, chlorobenzyl, methoxybenzyl, chlorobenzyl, trimethoxybenzoyl, pyrrolidino-acetyl, p-toluene-sulfonyl, phenylcarbamoyl, phenylthiocarbamoyl, 3-oxo-butyl, lower (C_{1-4}) alkyl-carbamoyloxy, phenethyl, dichloro-acetyl, 2-chlorophenoxy-2-methyl-propionyl or chlorophenyl-carbamoyl group.

The invention includes also within its scope the acid addition salts with inorganic or organic acids and the quaternary ammonium salts of the derivatives of the formula (I) and (II) when the latter are amines.

The invention relates also to a process for the preparation of compounds of the formulae (I) and (II) as defined above, comprising reacting a compound of the formula:



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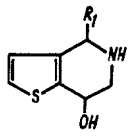


(IV)

in which R_1 has the above-defined meaning, with:

a) a halogen derivative of the formula Hal—R_3 in which R_3 is an alkyl of 1—18 carbon atoms, or aralkyl group optionally substituted with at least one halogen atom or alkoxy or nitro group, and Hal is halogen; or

b) a carboxylic acylating agent, such as an acid chloride or anhydride, in the case where R_3 is a carboxylic acyl radical optionally substituted with at least one halogen atom or amino, alkoxy, phenoxy, chlorophenoxy or pyrrolidino group; or

c) a sulfonic acid halide, in the case where R_3 is a sulfonyl group; or

d) an isocyanate or an isothiocyanate, in the case where R_3 represents an aminocarbonyl or aminothiocarbonyl group; or

e) an α,β-unsaturated ester, ketone or nitrile, in the case where R_3 is an alkyl or aralkyl group substituted with at least one ester, oxo or nitrile group, respectively; to give the derivatives of the formula (I) or (III) in which R_2 is hydrogen, and, if desired, reacting the derivative resulting from one of above steps a)—e) with:

f) an acylating agent of the formula $ClCOR_4$ or $(R_4CO_2)O$ in which R_4 is an alkyl, aralkyl or aryl radical, to give a derivative of the formula (I) or (II) in which R_2 is a carboxylic acyl group;

g) an isocyanate of the formula R_5NCO in which R_5 is an alkyl radical, to give a derivative of the formula (I) or (II) in which R_2 is an alkylaminocarbonyl radical; or

l) pyrrolidino (where the derivative initially obtained is a product of step (b) in which R_3 is a carboxylic acyl radical substituted by a halogen atom) to give a derivative of formula (I) or (II) in which R_3 is a carboxylic acyl radical substituted by a pyrrolidino group.

The starting compounds of the formuae (III) and (IV) in which R_1 is hydrogen are described, together with their preparation, in British patent application 29700/75 (Serial No. 1,486,646), and the compounds of the formulae (III) and (IV) in which R_1 is an alkyl group are described, together with their preparation, in British patent application 22087/76 (Serial No. 1,490,050).

The acid addition salts and the quaternary ammonium derivatives of the derivatives of the formulae (I) and (II) are prepared by conventional methods well known by those expert in the art.

The following non-limiting Examples are given to illustrate the preparation of the compounds of this invention.

EXAMPLE 1.

7-Hydroxy-5-p.nitrobenzyl-4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine (Derivative 1; Procedure a))

A mixture of 7-hydroxy-4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine hydrochloride (7 g; 36.52 mmoles), p-nitrobenzyl chloride (6.26 g; 36.52 mmoles), potassium carbonate (10.18 g) and ethanol (60 cc) is refluxed during 1.5 hours. After filtration of the inorganic salts, the filtrate is concentrated *in vacuo*. The residue is dissolved in chloroform and the organic phase is washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting oil is converted to the hydrochloride which is then recrystallised from 80% ethanol (M.p. = 200—210°C (dec.): yield: 52%).

EXAMPLE 2.

4-Hydroxy-6-pyrrolidinoacetyl-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (Derivative 2; Procedure b))

To a vigorously stirred mixture of 4-hydroxy-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine hydrochloride (12.35 g; 64.5 mmoles), sodium carbonate (13.7 g), water

(50 cc) and chloroform (150 cc), is added dropwise a solution of chloroacetyl chloride (7.3 g; 64.5 mmoles) in chloroform (50 cc). The mixture is stirred 2 hours at room temperature, after which the organic phase is decanted, washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residual oil is crystallized from isopropyl ether. The resulting crystals (M.p. = 103°C; yield: 72%) may be recrystallized from isopropanol-isopropyl ether (M.p. 107°C).

A mixture of the above product (9 g; 39 mmoles), pyrrolidine (2.8 g; 39 mmoles) and potassium carbonate (5.4 g) in dimethylformamide (50 cc) is heated during 3 hours at 100°C. After filtration of the inorganic salts, the filtrate is concentrated *in vacuo*. The residue is dissolved in methylene chloride, and the organic phase is then washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crystalline residue is recrystallized twice from ethyl acetate (M.p. = 117°C; yield: 42.5%).

EXAMPLE 3.

6-p.Chlorobenzoyl-4-hydroxy-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (Derivative 3; Procedure b))

To a vigorously stirred mixture of 4-hydroxy-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine hydrochloride (4.77 g; 25 mmoles), sodium carbonate (5.3 g), chloroform (25 cc), is added dropwise a solution of p-chlorobenzoyl chloride (4.4 g; 25 mmoles) in chloroform (25 cc). After stirring during one hour at room temperature, the organic phase is decanted, washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue is crystallized from isopropyl ether, filtered and recrystallized from isopropanol (M.p. = 148°C; yield: 53%).

EXAMPLE 4.

4-Hydroxy-6-p.toluenesulfonyl-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (Derivative 4; Procedure c))

To a vigorously stirred mixture of 4-hydroxy-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine hydrochloride (30 g; 0.156 moles), a saturated potassium carbonate solution (80 cc) and chloroform (200 cc) is added dropwise a solution of tosyl chloride (29.8 g; 0.156 moles) in chloroform (150 cc.) After stirring 2 hours at room temperature, the organic phase is decanted, washed with water, dried over sodium sulfate and concentrated *in vacuo*. The residue is recrystallized from isopropanol (M.p. = 130°C; yield: 86%).

EXAMPLE 5.

4-Hydroxy-6-N-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (Derivative 5; Procedure d))

To a solution of 4-hydroxy-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (5.6 g; 36.2 mmoles) in benzene (40 cc), is added dropwise a mixture of phenyl isocyanate (4.3 g; 36.2 mmoles) in benzene (10 ml). After stirring during 2 hours at room temperature, the resulting precipitate is filtered off, washed with ether and dried *in vacuo*. On recrystallization from ethanol, the desired product is obtained in a yield of 65% (M.p. = 200°C).

EXAMPLE 6.

4-Hydroxy-6-N-phenylthiocarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (Derivative 6; Procedure d))

To a solution of 4-hydroxy-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine (5.8 g; 37.4 mmoles) in benzene (60 cc) and 95% ethanol (30 cc) is added dropwise a mixture of phenyl isothiocyanate (5.05 g; 37.4 mmoles) in benzene (20 cc). After stirring during 2.5 hours at room temperature, the resulting precipitate is filtered off, washed with ether and dried *in vacuo* (M.p. = 168°C; yield: 79%).

EXAMPLE 7.

7-Hydroxy-5-(3-oxo-butyl)-4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine (Derivative 7; Procedure e))

A mixture of 7-hydroxy-4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine (5.7 g; 36.7 mmoles) and methyl vinyl ketone (2.6 g; 36.7 mmoles) in diethyl ether (10 cc) is stirred during 20 hours at room temperature. After concentration *in vacuo*, the residual oil is converted to the hydrochloride which is recrystallized from 95% ethanol (M.p. = 188—190°C; yield: 65%).

EXAMPLE 8.

7-Acetoxy-5-*o*-chlorobenzyl-4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine
(Derivative 8; Procedure f))

A mixture of 7-hydroxy-5-*o*-chlorobenzyl-4,5,6,7-tetrahydro-[3,2-c]-pyridine (6.7 g; 24 mmoles), acetic anhydride (14 cc) and dry pyridine (40 cc) is stirred during 3 hours at room temperature. The mixture is then poured over ice, made alkaline with concentrated ammonia and extracted with ether. The organic extracts are washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residual oil is converted to the hydrochloride which is recrystallized from ethanol-isopropanol (M.p. = 155—165°C; Yield: 52.5%).

EXAMPLE 9.

6-Methyl-4-N-propylcarbamoyloxy-4,5,6,7-tetrahydro-thieno-[2,3-c]-pyridine
(Derivative 9; Procedure g))

A mixture of 4-hydroxy-6-methyl-4,5,6,7-tetrahydro-thieno-[2,3-c]-pyridine (6 g; 35.4 mmoles), propyl isocyanate (3.9 g; 45.9 mmoles) triethylamine (3 g) and benzene (50 cc) is refluxed during 23 hours. The resulting material is concentrated *in vacuo* and the residue is dissolved in ether. The resulting solution is washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residual oil is converted to the maleate (M.p. = 167°C; yield: 70.5%).

Using procedures analogous with those described above, the following compounds were prepared:

Derivative 10: 4 - Hydroxy - 6 - methyl - 4,5,6,7 - tetrahydro - thieno[2,3-c]-pyridine, white crystals; M.p. = 94°C

Derivative 11: 6,7 - Dimethyl - 4 - hydroxy - 4,5,6,7 - tetrahydro - thieno - [2,3-c]-pyridine, maleate, cream-coloured crystals; m.p. = 120°C.

Derivative 12: 4 - Acetoxy - 6 - methyl - 4,5,6,7 - tetrahydro - thieno[2,3-c]-pyridine, maleate, pale cream-coloured crystals; m.p. 141°C.

Derivative 13: 4 - Acetoxy - 6,6 - dimethyl - 4,5,6,7 - tetrahydro - thieno[2,3-c]-pyridinium iodide; white crystals; m.p. = 260—262°C.

Derivative 14: 6 - Methyl - 4 - N - methyl-carbamoyloxy-4,5,6,7-tetrahydro-thieno-[2,3-c]-pyridine, maleate semi-hydrate; white crystals; m.p. = 160°C.

Derivative 15: 4 - N - Ethylcarbamoyloxy - 6 - methyl - 4,5,6,7 - tetrahydro-thieno[2,3-c]-pyridine, maleate semi-hydrate: white crystals; m.p. 144°C.

Derivative 16: 4 - Hydroxy - 6 - (3 - oxo - butyl) - 4,5,6,7 - tetrahydro-thieno[2,3-c]-pyridine; cream-coloured crystals; m.p. 90°C.

Derivative 17: 4 - Acetoxy - 6 - ß - phenethyl - 4,5,6,7 - tetrahydro - thieno-[2,3-c]-pyridine, maleate; white crystals; m.p. 139°C.

Derivative 18: 4 - Acetoxy - 6 - *o* - chlorobenzyl - 4,5,6,7 - tetrahydro - thieno-[2,3-c]-pyridine, hydrochloride; grey crystals; m.p. = 145—150°C.

Derivative 19: 6 - *o* - Chlorobenzyl - 4 - hydroxy - 7 - methyl - 4,5,6,7 - tetrahydro-thieno[2,3-c]-pyridine, hydrochloride; white crystals; m.p. = 180—183°C.

Derivative 20: 6 - *p* - Chlorobenzyl - 4 - hydroxy - 4,5,6,7 - tetrahydro - thieno-[2,3-c]-pyridine, maleate; creamy-white crystals; m.p. = 158°C.

Derivative 21: 4 - Acetoxy - 6 - *p* - methoxybenzyl - 4,5,6,7 - tetrahydrothieno-[2,3-c]-pyridine, maleate; white crystals; m.p. = 162°C.

Derivative 22: 4 - Hydroxy - 6 - *o* - nitrobenzyl - 4,5,6,7 - tetrahydro - thieno-[2,3-c]-pyridine; hydrochloride; pale yellow crystals; m.p. = 180°C (decomposition).

Derivative 23: 4 - Hydroxy - 7 - methyl - 6 - *o* - nitrobenzyl - 4,5,6,7 - tetrahydro-thieno[2,3-c]-pyridine; beige crystals; m.p. = 195°C (decomposition).

Derivative 24: 4 - Hydroxy - 6 - *p* - nitrobenzyl - 4,5,6,7 - tetrahydro - thieno-[2,3-c]-pyridine, maleate; pale yellow crystals; m.p. = 175—177°C.

Derivative 25: 4 - Acetoxy - 6 - dichloroacetyl - 4,5,6,7 - tetrahydro - thieno-[2,3-c]-pyridine; white crystals; m.p. = 125°C.

Derivative 26: 4 - Hydroxy - 6 - (3,4,5 - trimethoxy - benzoyl) - 4,5,6,7 - tetra-hydro-thieno[2,3-c]-pyridine; m.p. = 158°C.

Derivative 27: 6 - (2 - *p* - chlorophenoxy - 2 - methyl - propionyl) - 4 - hydroxy-4,5,6,7 - tetrahydro - thieno[2,3-c] - pyridine; cream-coloured material; m.p. = 127°C.

Derivative 28: 6 - (N - *p* - Chlorophenylcarbamoyl) - 4 - hydroxy - 4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine; beige crystals; m.p. = 170°C.

Derivative 29: 7 - Hydroxy - 5 - methyl - 4,5,6,7 - tetrahydro - thieno[3,2-c]-pyridine, maleate; white crystals; m.p. = 145°C.

Derivative 30: 5 - *o* - Chlorobenzyl - 7 - hydroxy - 4,5,6,7 - tetrahydro - thieno-[3,2-c]-pyridine, hydrochloride; white material; m.p. = 195—215°C.

Derivative 31: 7 - Hydroxy - 5 - *o* - nitrobenzyl - 4,5,6,7 - tetrahydro - thieno-[3,2-c]-pyridine, pale yellow crystals; m.p. = 125°C.

The results of toxicological and pharmacological tests reported below demonstrate the useful activities of the derivatives of this invention, particularly their vaso-dilatator activity and their inhibiting activity on blood plate aggregation.

Thus, the invention includes also within its scope a therapeutic composition having in particular an anti-inflammatory action, and an inhibiting activity on blood plate aggregation comprising, as active ingredient, a derivative of the formula (I) or (II) or a therapeutically acceptable acid addition salt or quaternary ammonium derivative thereof, and a therapeutically administrable carrier.

TOXICOLOGICAL INVESTIGATION

Said investigation demonstrated the low toxicity and the good tolerance of the derivatives of this invention.

For indicative purposes, the LD_{50}/24 hours/kg body weight in mice, calculated according to the method of Miller and Tainter (Proc. Soc. Exptl. Biol. Med. 1944, 57, 261), by the intravenous route, is 90 mg for derivative 1, 225 mg for derivative 2, 260 mg for derivative 7, 200 mg for derivative 8, 220 mg for derivative 9, 340 mg for derivative 10, 220 mg for derivative 11, 260 mg for derivative 12, 280 mg for derivative 14, 270 mg for derivative 15, 250 mg for derivative 16, 110 mg for derivative 20, 245 for derivative 21, 150 mg for derivative 24 and 350 mg for derivative 29.

PHARMACOLOGICAL INVESTIGATION

The pharmacological tests demonstrate that the derivatives of this invention possess anti-inflammatory activities and an inhibiting activity on blood platelet aggregation.

1. Anti-inflammatory action

a) Localised carrageenin-induced edema method:

A 1% carrageenin solution (1 ml) is injected in the metatarsalflexor muscles of the right hind limb of rats at time 0. The animals of the treated group are additionally administered orally 100 mg/kg of the test derivative, respectively one hour prior to and then simultaneously with the phlogogenic agent, and then one hour and 2.5 hours thereafter. The percent anti-inflammatory activity, as a function of time, is determined by measurements effected with a ROCH micrometer at times 0, one hour, two hours, three hours and five hours after carrageenin administration. The results obtained are given in the following Table I:

TABLE I

Derivative	Percent anti-inflammatory activity after 1 hour	after 2 hours	after 5 hours
2	35	48	55
5	41	50	55
7	42	56	60
12	37	50	58
18	34	44	57
26	36	49	54
29	45	55	61

b) Ovalbumin-induced systemic edema method

Rats are administered a simultaneous intraperitoneal injection of 1 ml ovalbumin and 0.5 ml of a 1% aqueous Evans Blue solution. The animals of the treated group are additionally administered orally 100 mg/kg of the test derivative, one hour prior to ovalbumin administration and simultaneously with said ovalbumin administration. The intensity of the phenomenon thus induced is scored according to a scale of from 1 to 5, according to the progress of the inflammatory syndrome. The determinations are effected after 2 hours and after 3 hours. Thus are determined the mean intensity of the edema and the percent decrease of the edema reaction. The results obtained are given in following Table II:

TABLE II

Derivative	Percent decrease After 2 hours	Percent decrease After 3 hours
2	38	44
5	33	43
7	41	52
12	46	59
18	42	58
26	51	63
29	49	59

2. Inhibiting activity on blood platelet aggregation

Rat plasma, prepared to contain 600,000 ± 20,000 blood platelets per mm3 is normally cloudy. Addition of adenosine diphosphate induces blood plate aggregation and, thus, and increase of the light transmission, a phenomenon readily measurable with a spectrophotometer. When the same test is effected with a plasma prepared from the blood of an animal which has been administered 100 mg/kg of a derivative having an inhibiting effect on blood plate aggregation, there is no aggregation of the blood plates and the serum remains cloudy. The turbidimetric assay effected with a spectrophotometer provides a measure of the inhibiting activity on blood plate aggregation of the test derivatives.

The tests carried out with groups of five rats (three controls and two treated animals) show that the compounds of this invention induce a substantial percent inhibition on blood plate aggregation, said percent inhibition being respectively 92% for derivative 4, 89% for derivative 5, 86% for derivative 9, 88% for derivative 15, 74% for derivative 18, 93% for derivative 22, 84% for derivative 25 and 88% for derivative 29.

It is apparent from the toxicological and pharmacological investigations reported above, that the derivatives of this invention are endowed with a good tolerance and that they possess a valuable anti-inflammatory activity and a valuable inhibiting activity on blood plate aggregation.

The composition of this invention may be formulated, for oral administration, as tablets, coated tablets, capsules, drops or syrups. It may also be formulated as suppositories for rectal administration and as injectable solutions for parenteral administration.

Each unit dose contains advantageously 0.025—0.500 g active ingredient, the daily dosage regimen varying within the range from 0.025 g to 1 g active ingredient, according to the age of the patient and the severity of the condition to be treated.

Non-limiting Examples of pharmaceutical formulations of the composition of this invention are given below.

EXAMPLE 10.
TABLETS

Derivative n°5	0.100	g
Starch	0.025	g
Potato starch	0.010	g
Talc	0.005	g
Magnesium stearate	0.005	g

EXAMPLE 11.
COATED TABLETS

CORE	Derivative n°9	0.075	g
	Calcium carbonate	0.010	g
	Magnesium stearate	0.010	g
	Talc	0.005	g
COATING	Gum tragacanth	0.003	g
	Shellac	0.002	g
	Rosin	0.002	g
	Glucose	0.010	g
	White wax	0.001	g
	New coccine	traces	
	Sugar, sufficient for 1 coated tablet		

EXAMPLE 12.
CAPSULES

Derivative n°18	0.125	g
Talc	0.005	g
Magnesium stearate	0.005	g
Starch	0.005	g

EXAMPLE 13.
SYRUP

Derivative n°22	2.00	g
Sweetened and flavoured excipient, sufficient for	100	ml

EXAMPLE 14.
INJECTABLE SOLUTION

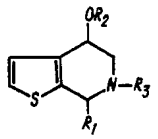
Derivative n°29	0.100	g
Isotonic solution, sufficient to make	2	ml

The composition of this invention is usefully administrable for the treatment of the various stages of inflammation. It is applicable in chronic inflammatory rheumatism, degenerative rheumatism, in abarticular conditions, in oto-rhino-laryngology, in stomatology, in post-operative surgery and in traumatology.

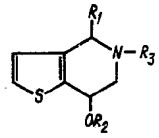
In view of its inhibiting effect on blood platelet aggregation, it is administrable to patients suffering from disorders of the cerebral and peripheral circulatory system.

WHAT WE CLAIM IS:—

1. Tetrahydrothieno-pyridine derivatives having the formula:



(I)



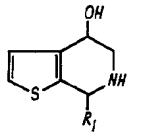
(II)

in which R_1 represents hydrogen or an alkyl group having 1—6 carbon atoms; R_2 represents hydrogen or a carboxylic acyl or alkylamino-carbonyl group; and R_3 represents an alkyl of 1—18 carbon atoms, or aralkyl group optionally substituted with at least one ester, oxo or nitro group, halogen atom or alkoxy or nitro group; a carboxylic acyl radical optionally substituted with at least one halogen atom or amino, alkoxy, phenoxy, chlorophenoxy or pyrrolidino group; of a sulfonyl, aminocarbonyl or aminothiocarbonyl group; their acid addition salts and their quaternary ammonium salts.

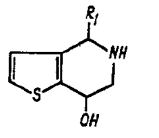
2. Derivatives as claimed in claim 1, wherein R_2 is selected from hydrogen, the acetyl group and a C_{1-4} alkyl-carbamoyl group.

3. Derivatives as claimed in claim 1 or 2, wherein R_3 is a C_{1-4} alkyl, nitrobenzyl, chlorobenzyl, methoxybenzyl, chlorobenzyl, trimethoxybenzoyl, pyrrolidinoacetyl, p.toluene-sulfonyl, phenylcarbamoyl, phenylthiocarbamoyl, 3-oxo-butyl, C_{1-4} alkyl-carbamoyloxy, phenethyl, dichloroacetyl, 2-chlorophenoxy-2-methyl-propionyl or chlorophenyl-carbamoyl group.

4. A process for the preparation of derivatives as defined in any one of claims 1—2, comprising reacting a compound of the formula:



(III)



(IV)

in which R_1 is as defined in claim 1, with:

a) a halogen derivative of the formula Hal—R_3 in which Hal is halogen and R_3 is an alkyl of 1—18 carbon atoms, or aralkyl group optionally substituted with at least one halogen atom or alkoxy or nitro group; or

b) a carboxylic acylating agent such as an acid chloride or anhydride, in the case where R_3 is a carboxylic acyl radical optionally substituted with at least one halogen atom or amino, alkoxy, phenoxy, chlorophenoxy or pyrrolidino group; or

c) a sulfonic acid halide, in the case where R_3 is a sulfonyl group; or

d) an isocyanate or isothiocyanate, in the case where R_3 represents an aminocarbonyl or aminothiocarbonyl group; or

e) an α,β-unsaturated ester, ketone or nitrile, in the case where R_3 is an alkyl or aralkyl group substituted with at least one ester, oxo or nitrile group, respectively;

to give the derivatives of the formulae (I) and (II) in which R_2 is hydrogen, and, if desired, reacting a derivative obtained in one of the steps (*a*)—(*e*) above with:

f) an acylating agent of the formula $ClCOR_4$ or $(R_4CO_2)O$ in which R_4 is an alkyl, aralkyl or aryl radical, to give a derivative of the formula (I) or (II) in which

R_2 is a carboxylic acyl group; g) an isocyanate of the formula R_5NCO, in which R_5 is an alkyl radical, to give a derivative of the formula (I) or (II) in which R_2 is an alkylaminocarbonyl radical; or h) pyrrolidine (where the derivative initially obtained is a product of step (b) in which R_3 is a carboxylic acyl radical substituted by a halogen atom) to give a derivative of formula (I) or (II) in which R_3 is a carboxylic acyl radical substituted by a pyrrolidino group).

5. Therapeutic composition comprising, as active ingredient, a derivative of the formula (I) or (II) as defined in claim 1 or a pharmaceutically acceptable acid addition salt or a quaternary ammonium derivative thereof, and a therapeutically administrable carrier.

6. Composition as claimed in claim 5, in unit dosage form, each unit dose containing 0.025—0.500 g active ingredient.

7. Thieno-pyridine derivatives as claimed in claim 1, as herein specifically disclosed.

8. Process for the preparation of thieno-pyridine derivatives as claimed in claim 1, substantially as described with reference to Examples 1—9.

9. Therapeutic composition as claimed in claim 5, substantially as described with reference to Examples 10—14.

10. A process for the preparation of compounds of general formula I or II substantially as herein described.

11. Compounds of general formula I or II as claimed in claim 1 whenever prepared by a process claimed in any one of claims 4, 8 and 10.

12. A therapeutic composition comprising a compound of formula I or II as claimed in claim 1 substantially as herein described.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.